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EXAMINER

HILL, KEVIN KAI

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/815,262	Applicant(s) ENGELHARDT ET AL.	
	Examiner KEVIN K. HILL	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,9-25,27,29-46,48-51,53,55-59 and 61-64 is/are pending in the application.
- 4a) Of the above claim(s) 3,25,27,29-42,45,51,53 and 55-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-7,9-24,43,44,46,48-50 and 61-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>September 23, 2008</u> . | 6) <input type="checkbox"/> Other: _____ |

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Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 23, 2008 has been entered.

Election/Restrictions

Applicant has elected with traverse the invention of Group I, Claims 1-32 and 43-60, drawn to a method of enhancing recombinant adeno-associated virus (rAAV) transduction in mammalian cells, comprising contacting the mammalian cells with at least one agent in an amount effective to additively or synergistically enhance rAAV transduction.

Within Group I, Applicant has further elected the restricted subgroup "A", wherein the at least two agents additively enhance rAAV transduction.

Within Group I, Applicant has elected the following species:

- a) the agent interaction effect species "ii", wherein the agent alters cellular uptake of rAAV, as recited in Claims 4 and 46.
- b) the biological functionality associated with an agent species "vi", wherein the agent modulates rAAV processing in the cell, as recited in Claims 28, 43 and 54.
- c) the agent category species "xiii and xiv", wherein the agents are an antibiotic and a chemotherapeutic, as recited in Claims 8 and 47.
- d) the biological functionality species "doxil" and "LLnL", as recited in Claims 21 and 60. However, upon further examination of the subject matter, the Examiner has extended the species under examination to include doxorubicin.
- e) the cell type species "mammalian lung cell", as recited in Claims 16 and 48.
- f) the polypeptide biological functionality species "cystic fibrosis transmembrane conductance regulator (CFTR)", as recited in Claim 20, wherein CFTR is found in both rAAVs.

Amendments

Applicant's response and amendments, filed July 23, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 8, 26, 28, 47, 52, 54 and 60, withdrawn Claims 3, 25, 27, 29-42, 45, 51, 53 and 55-59, amended Claims 1, 21, 25, 27, 29-32, 43, 51, 53 and 55-59, and added new claims, Claims 63-64.

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Claims 3, 25, 27, 29-42, 45, 51, 53 and 55-59 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50 and 61-64 are under consideration.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 23, 2008 response will be addressed to the extent that they apply to current rejection(s).

Priority

Applicant's claim for the benefit of a prior-filed application parent provisional applications 60/459,323, filed on March 31, 2003 and 60/512,347, filed on October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on September 23, 2008, that has been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Specification

1. **The prior objection to the disclosure is withdrawn** in light of Applicant's amendment to the Brief Description of the Drawings, papers filed July 23, 2008, to more clearly refer to each panel of the Drawings filed October 29, 2004.

Claim Objections

2. **The prior objection to Claims 1 and 21 are withdrawn** in light of Applicant's amendments to the claims, thereby rendering the objections moot.

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3. **Claims 43, 61 are objected to because of the following informalities:** the term “AAV” (Claim 43, line 6; Claim 61, line 1) is not concordant with the preamble of the claim "enhance rAAV" (Claim 43, line 1). See, for example, Claim 1 (lines 1 and 3-4).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 1-2, 4-7, 9-24, 43-44, 46 and 48-50 and 61-62 under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements **is withdrawn** in light of Applicant's amendments to the claims, that the first agent selected from the group consisting of “a chemotherapeutic, a lipid lowering agent, an antibiotic or a tannic acid” and the second agent having proteasome proteolytic activity “each enhance intracellular rAAV transduction”, Applicant's argument that the second agent inhibits proteasome proteolytic activity and enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome, and that the agent recited in claims 4 and 46 is a third agent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, 61-62 stand and 63-64 are newly rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the Office Action mailed April 23, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 23, 2008.

The claimed invention is directed to a method for enhancing recombinant adeno-associated virus (rAAV) transduction of a mammalian cell. At issue for the purpose of written description requirements, are:

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- a) the identity and structure of the agents that enhances “intracellular rAAV transduction in an amount effective to additively or synergistically [“or at least additively”] enhance rAAV transduction” recited in claims 1 and 43;
- b) the identity and structure of the agent that alters “uptake of rAAV at the cell membrane” as recited in claims 4 and 46; and
- c) the identity and structure of the agent that enhances “AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome”, as recited in claims 43 and 61.

When the claims are analyzed in light of the specification, instant invention recites/encompasses a genus of structurally diverse compositions that are known in the art to possess mechanistically distinct biochemical activities.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed.” (See *Vas-cath* at page 1116).

With respect to those agents that enhance intracellular rAAV transduction, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses that tri-peptide proteasome inhibitors such as LLnL and Z-LLL, and agents such as doxorubicin, tannic acid, and cisplatin can enhance rAAV transduction (pg 5, lines 30-31; pg 80, lines 8-13). However, the specification discloses that while DNA metabolism agents, e.g. etoposide, hydroxyurea and camptothecin enhance transduction when utilized singularly, said agents produce no additive or synergistic effects when used in combination (pg 6, lines 3-8; pg 67, lines 1-2). Only the combination of LLnL and doxorubicin is disclosed to achieve at least additive, and more specifically, synergistic effects to enhance intracellular rAAV transduction (pg 81, lines 20-21).

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. While

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Applicant claims an enormous genus of structurally diverse compounds to be used "in an amount to additively or synergistically" enhanced intracellular rAAV transduction, the specification fails to disclose a common core structure or identifying characteristic of the plurality of agents necessary and sufficient to functionally achieve via combinatorial use "in an amount to additively or synergistically" enhanced intracellular rAAV transduction such that the ordinary artisan would know *a priori* that one or more given agents would perform the claimed function. Rather, only the combination of LLnL and doxorubicin is disclosed to functionally achieve the claimed properties.

With respect to those agents capable of altering the cellular uptake of rAAV, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification fails to disclose any species of compounds necessary and sufficient to alter the cellular uptake of rAAV. The specification discloses that neither LLnL nor doxorubicin alters cellular uptake of AAV (Applicant's argument, papers filed February 4, 2008, pg 17, lines 26-27). See also where the specification discloses that viral binding and internalization ["uptake"] are not affected by LLnL treatment (pg 70, line 1). While combinatorial use of LLnL and EGTA "substantially increased the amount of virus internalized from apical surface", "EGTA treatment alone only slightly increased persistence of AAV DNA or AAV-mediated gene expression" (pg 72, lines 7-9). Thus, neither LLnL nor EGTA are disclosed as an agent capable of fulfilling the required function "of altering the cellular uptake of rAAV.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. Applicant claims an enormous genus of structurally diverse compounds that share no common core structure or identifying characteristic necessary and sufficient to functionally achieve altering the cellular uptake of rAAV such that the ordinary artisan would know *a priori* that an agent that would perform the claimed function.

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With respect to those agents that enhance AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. However, the specification does not disclose the complete structure of any species of the genus, nor other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. Applicant claims an enormous genus of structurally diverse compounds that share no common core structure or identifying characteristic necessary and sufficient to functionally achieve enhanced AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome such that the ordinary artisan would know *a priori* that an agent that would perform the claimed function.

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

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Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Accordingly, given that the specification does not adequately disclose the complete structure of the exceptionally broadly-defined “agent” genus that is to perform the recited functions, specifically a) the identity and structure of the agent(s) that enhances “intracellular rAAV transduction in an amount effective to additively or synergistically [“or at least additively”] enhance rAAV transduction”; b) the identity and structure of the agent(s) that alters “uptake of rAAV at the cell membrane”; and c) the identity and structure of the agent(s) that enhances “AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome”, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant argues that the claims recite relevant, identifying characteristics for the agents, i.e., each agent alone enhances intracellular rAAV transduction, and one agent is a chemotherapeutic, a lipid lowering agent, an antibiotic or a tannic acid, e.g., epoxomicin, doxorubicin, daunorubicin, idarubicin, epirubicin, aclarubicin, or simvastatin and the other agent inhibits proteasome proteolytic activity or enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome.

Applicant's argument(s) has been fully considered, but is not persuasive. An adequate written description of a chemical invention also requires a precise definition, such as by

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structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). In the instant case, and unfortunately for Applicant, the substantive issue discussed in the prior Office Action and iterated above, is that the functional characteristic(s) of each agent **has not** been coupled with a known or disclosed correlation between function and structure. The specification does not provide a sufficient description of a representative number of species, if any, of each agent category that fulfills the recited functions.

6. **Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50 and 61-62 stand and 63-64 are newly rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the Office Action mailed April 23, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 23, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not

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disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claim is exceptionally large for encompassing methods of enhancing the transduction of an enormous genus of recombinant adeno-associated viruses (rAAV) to an enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*, the method comprising the use of an enormous genus of structurally diverse agents recited to perform a broad genus of distinctly different cell biological effects so as to enhance rAAV transduction in the target cell. Applicant broadly contemplates the term ‘viral transduction’ to include a broad genus of distinctly different and mutually exclusive cell biological processes, such as endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg 8, lines 23-27).

The inventive concept in the instant application is that rAAV transduction of a mammalian host cell may be enhanced by administering one or more compounds, e.g. the proteasome inhibitor LLnL or the antibiotic/chemotherapeutic compound doxorubicin.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of one of ordinary skill in the art of recombinant adeno-associated viral vector design and delivery is considered to be high.

The prior art is silent with respect to the administration of agents, particularly the elected embodiments DOXIL® and LLnL, to enhance rAAV transduction. The claimed methods recite the administration of agents to alter distinctly different cell biological processes to enhance transduction. However, Goncalves (Virology J. 2: 43; 17 pages, 2005) teaches that the events and processes that regulate the trafficking of AAV particles into the nucleus are still not fully understood (pg 5 of 17). An increasingly important area in the development of AAV as a vector concerns the engineering of altered cell tropisms to narrow or broaden rAAV-mediated gene delivery and to increase its efficiency in tissues refractory to AAV2 infection. Cells can be poorly transduced by prototype rAAV2 not only because of low receptor content but also owing to impaired intracellular virion trafficking and uncoating or single-to-double strand genome conversion. Thus, considering that these processes depend either directly or indirectly on capsid conformation, cell targeting strategies determine not only the cell type(s) with which the vector interacts but also critically affect the efficiency of the whole gene transfer process. (pg 7 of 17) Several of these approaches rely on the modification by chemical, immunological or genetic means of the AAV2 capsid structure endowing it with ligands that interact with specific cell surface molecules. Another route to alter rAAV tropism exploits the natural capsid diversity of newly isolated serotypes by packaging rAAV2 genomes into capsids derived from other human or non-human AAV isolates. To this end, up until now, most researchers employ hybrid *trans*-complementing constructs that encode *rep* from AAV2 whereas *cap* is derived from the serotype

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displaying the cell tropism of choice. For example, experiments published recently using rAAV2 genomes pseudotyped with coats from AAV6 and AAV8 revealed stunning gene transfer efficiencies when these vectors were administered alone at high doses or in combination with a blood vessel permeating agent.

Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) teach that the administration of tripeptide protease inhibitors, e.g. LLnL, increase rAAV gene delivery (pg 1573, Abstract). However, this phenomenon is not universal in that the proteasome inhibitor did not affect transduction of skeletal or cardiac muscle, indicating that tissue-specific ubiquitination of viral capsid proteins interfere with rAAV-2 transduction.

Given the limited teachings in the art regarding the co-administration of two or more compounds designed to specifically alter particular cell biological processes to intentionally enhance rAAV transduction of an enormous genus of mammalian cell types *in vitro*, *ex vivo* and *in vivo*, one of ordinary skill in the art would reasonably conclude that a high degree of unpredictability regarding an *a priori* determination that any specific compound will enhance viral transduction. It necessarily follows that the art recognizes significant unpredictability for any two agents to yield an additive interaction to enhance viral transduction. Furthermore, there is a clear contradiction between the art and the instant specification regarding the biochemical properties of the doxorubicin and DOXIL® as per the inhibition of proteasome proteolytic activity.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The method steps of the invention require the artisan to administer a plurality of compounds (or agents), wherein each compound is capable of fulfilling a recited function, namely i) alter cellular uptake of rAAV, ii) modulate rAAV processing in the cell, and iii) processing in intracellular compartments. Applicant broadly contemplates the term viral transduction to include endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg 8, lines 23-27). However, neither the claims nor the specification disclose explicitly which compound performs the recited function(s).

The lack of correlation in the specification regarding the particular cell biological activity(ies) affected by each contemplated agent necessarily fails to provide sufficient guidance to the artisan so as to perform the claimed method(s). In the instant case, Applicant has elected the agent structure species “DOXIL®” and “LLnL”, and the agent function species “alters cellular uptake of rAAV” and “modulates rAAV processing in the cell”. The specification discloses DOXIL® to be a chemotherapeutic agent (pg 79, line 20) and is disclosed to enhance rAAV transduction (pg 82, line 31). DOXIL® is the liposomal formulation of doxorubicin (pg 80, line 17) that is an approved antibiotic (pg 9, line 25) and chemotherapeutic agent (pg 79, line 20). The specification also discloses that “LLnL” is a proteasome inhibitor that can enhance transduction (pg 5, line 30), but acts at a point distal to (that is, after) virus binding and entry (pg 70, line 8). LLnL and doxorubicin synergistically enhance rAAV transduction *in vitro*, as measured by reporter gene expression 1000-fold, while individually, doxorubicin and LLnL enhanced rAAV reporter gene expression 100- and 10-fold, respectively (pg 12, lines 8-10).

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However, the claims lack enablement because the specification fails to disclose the identity and structure of the agent(s) that alters “uptake of rAAV at the cell membrane” and the agent(s) that enhances “AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome”, any working example of said agent(s) performing said function(s), nor the proper dosage that said agent(s) should be administered to achieve a specific cell biological effect(s). There is a lack of data to demonstrate that a specific agent alters “uptake of rAAV at the cell membrane” or enhances “AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome”.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the administration of an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes will yield an additive functional interaction so as to enhance rAAV transduction of enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of enhancing rAAV transduction comprising contacting a mammalian cell with an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes constitute such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant argues that:

a) it would not be undue experimentation for the artisan to screen for compounds that at least additively enhance rAAV transduction. Evidence that screening numerous compounds to detect the effect of the compound on virus infection or replication is within the skill of the art is provided in the abstracts for Cheng et al (2004) and Dhanak et al (2002);

b) rAAV, chemotherapeutics, lipid lowering agents, antibiotics and tannic acid have each been used *in vivo*; and

c) while the process regulating AAV trafficking into the nucleus may not be fully understood (Goncalves), the specification discloses agents that modulate AAV trafficking into the nucleus. Goncalves does not relate to the use of exogenously administered agents to enhance AAV transduction and so does not evidence the level of (or lack of) predictability in the relevant art.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), both Cheng et al and Dhanak et al are drawn to assaying a specific target enzyme activity, i.e. a protease that cleaves beta-galactosidase or an RNA-dependent RNA polymerase, not cell biological process such as viral uptake and intracellular trafficking. Thus, these references are not considered commensurate in scope to the instantly claimed invention because they do not establish that the artisan would know what specific enzyme must be targeted to screen for compounds having the desired activity, e.g. enhancement or inhibition of a specific enzyme that would clearly result in the instantly claimed function(s), specifically: i) enhance "intracellular rAAV transduction", ii) alter "uptake of rAAV at the cell membrane", and iii) enhance "AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome".

With respect to b), Applicant has failed to address the substantive issue, which is the **combined use** of at least two or more agents having distinctly different functional activities to achieve a desired effect via an at least additive, if not synergistic interaction. The specification only discloses that LLnL and doxorubicin achieve a synergistic interaction to enhance rAAV transduction.

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Applicant is respectfully reminded that it is generally recognized in the art that biological compounds often react unpredictably under different circumstances (*Nationwide Chem. Corp. v. Wright*, 458 F. supp. 828, 839, 192 USPQ95, 105(M.D. Fla. 1976); Affd 584 F.2d 714, 200 USPQ257 (5th Cir. 1978); *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)). The relative skill of the artisan or the unpredictability of the pharmaceutical art is very high. Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved" (See *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970))), the skilled artisan would have not known how to extrapolate the results provided in the instant specification as per the combined use of LLnL and doxorubicin to the use of the enormous and structurally varied genus of agents in one or more combinations so as to achieve an at least additive if not synergistic interaction to enhance rAAV transduction.

The artisan would essentially have to experiment by trial and error to determine which compounds possesses the desired activity alone, specifically i) enhance "intracellular rAAV transduction", ii) alter "uptake of rAAV at the cell membrane", and iii) enhance "AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome", and then determine by trial and error each combinatorial permutation to identify which compound(s) is capable of performing the recited function(s) in combination with one or more other compounds, so as to essentially invent for themselves a method of enhancing rAAV transduction *in vitro*, *ex vivo* and *in vivo*. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

With respect to c), it is unclear how Applicant would consider the lack of understanding of a biological process to not establish unpredictability in the art (Goncalves). Applicant is essentially arguing that one can predict what one does not know. Applicant is claiming the combinatorial use of a genus of agents that i) enhance "intracellular rAAV transduction", ii) alter "uptake of rAAV at the cell membrane", and iii) enhance "AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of

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the viral genome”, for which the identity of agents fulfilling functional properties (ii) and (iii) are not disclosed, and only one embodiment of (i), doxorubicin in combination with LLnL, is actually reduced to practice. The Examiner disagrees with Applicant's position that one of ordinary skill in the art would know how to use said enormous genus of undisclosed agents alone and in combination at the time of filing of the instant application (March, 2003) when two years afterwards Goncalves (2005) teach that the ordinary artisan does not understand how rAAV intracellular trafficking proceeds.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The use of an enormous genus of undisclosed agents having functional properties that are not recognized in the art as per the transduction of rAAV is considered a “germ of an idea”.

Furthermore, in the absence of explicitly pointing out where (page, line) the limitations “agents that modulate AAV trafficking into the nucleus” are taught, the instant argument is incomplete and unpersuasive. The Examiner is only able to find two specific agent species that *may* [emphasis added] support Applicant's argument, for which Applicant's own disclosure establishes inconclusive, and at best hypothesis-generating, findings. The specification discloses, for example, that “doxorubicin *may* [emphasis added] facilitate transportation into the nucleus” (pg 9, line 26), and that “LLnL *may* [emphasis added] be accelerating processing and routing of the virus to the nucleus” (pg 70, line 12). Thus, the Examiner maintains the position that Goncalves is art that establishes continued unpredictability germane to the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 1-2, 4-7, 9-23, 43-44, 46, 48-50 and 61 stand, and Claims 63-64 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS), Maitra et al (Am. J. Physiol. Cell Physiol. 280:C1031-C1037, 2001; *of record) and Englehardt (U.S. Patent 6,436,392; *of record).

The Examiner provides Mikulski (U.S. Patent 6,290,951) and Oberdorf et al (Biochemistry 40(44):13397-13405, 2001) as evidentiary references.

This rejection is maintained for reasons of record in the Office Action mailed April 23, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 23, 2008.

Determining the scope and contents of the prior art.

Duan et al teach a method of enhancing adeno-associated virus 2 (rAAV-2) transduction, the method comprising contacting human lung cells with rAAV and at least two different agents, wherein one of the agents, specifically, the tripeptide protease inhibitor LLnL, inhibits proteasome proteolytic activity, wherein LLnL modulates rAAV processing in the cell (pg 1582, col. 1, lines 5-7; col. 2, lines 15-17). LLnL enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis (pg 1581, col. 1). The AAV vector comprises a marker gene, specifically Green Fluorescent Protein (GFP) (pg 1574, Methods, see also references cited therein). The cells were pretreated with the proteasome protease inhibitors prior to contact with the rAAV (pg 1575, col. 2, Transduction). Duan et al also teach that the administration of LLnL after the cells are contacted with the virus also results in enhanced transgene expression (pg 1580, col. 2).

Duan et al do not teach the method to comprise the use of the agent doxorubicin. However, at the time of the invention, Kiyomiya et al taught that adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor.

Duan et al do not teach the method further comprising a second rAAV comprising a first DNA segment comprising a 5' ITR linked to a second DNA segment comprising a heterologous DNA which has sequences that are different than the sequences in the second DNA segment of

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the first recombinant DNA molecule linked to a third DNA segment comprising a 3' ITR. However, at the time of the invention, Englehardt disclosed methods of transducing mammalian cells comprising at least two different rAAV vectors, wherein the second DNA segment comprising a heterologous sequence of the first vector is different from the second DNA segment comprising a heterologous sequence of the second vector. Englehardt disclosed wherein the second DNA segment of the first recombinant DNA molecule comprises a portion of an open reading frame for a gene product, optionally operably linked to at least one transcriptional regulatory element, and a splice donor site 3' to the portion of the open reading frame, and wherein the second DNA segment of the second recombinant DNA molecule comprises a splice acceptor site 5' to the remainder of an open reading frame, which together with the second DNA segment of the first recombinant DNA molecule encodes a functional gene product, substantially as claimed (col. 4, line 47-col. 5, line 25), wherein the transcriptional regulatory element comprises a promoter and an enhancer (col. 16, lines 1-6), and wherein the functional gene product is a therapeutic polypeptide, e.g. cystic fibrosis transmembrane conductance regulator (CFTR) (col. 3, line 30; col. 49, lines 23-48). Englehardt disclosed that the rAAV vectors form heteroconcatamers, which increased persistence of transgene expression, and thereby enhances the expression of the functional gene product (col. 3, lines 39-41; col. 10, lines 24-26).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, virology, cellular infection with rAAV, and protocols and reagents useful for the treatment of disease. Therefore, the level of ordinary skill in this art is high.

Duan et al teach that differentiated airway epithelia are extremely resistant to rAAV infection, thereby inhibiting therapeutic gene delivery of wildtype CFTR genes. The ubiquitin-proteasome pathway is involved in rAAV-2 transduction, and that when proteasome function was inhibited, a substantial augmentation in rAAV-2 mediated transgene expression was observed. Proteasome systems are known to modulate the intracellular processing of many foreign molecules, including viruses. LLnL substantially increased rAAV transduction from the mucosal surface (Duan et al; pg 1579, col.s 1-2, joining ¶). Kiyomiya et al teach that doxorubicin is also a proteasome protease inhibitor. Maitra et al teach that low-dose doxorubicin significantly increases the functional cell-surface expression of CFTR and the most common CFTR mutation, DeltaF508. Restoration of functional CFTR expression to 10% of normal levels would be sufficient to ameliorate the symptoms of the disease *in vivo* (pg C1031, col. 20). Thus, administration of doxorubicin would be reasonably expected to achieve two therapeutic mechanisms in the treatment of Cystic Fibrosis, namely increased expression of CFTR to ameliorate the symptoms of the disease and enhance the rAAV viral transduction as per inhibition of the proteasome protease.

Neither Duan et al, Kiyomiya et al nor Maitra et al teach the formulations of doxorubicin and LLnL to achieve an additive or synergistic enhancement of rAAV transduction. However, it is well within the skill of the ordinary artisan to vary the respective concentrations of the first

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and second agents as part of routine optimization so as to identify conditions that would result in additive or synergistic enhancement by at least 2-fold to at least 10-fold relative to transduction of a corresponding mammalian cell contacted with the rAAV and one of the agents or no agent, as demonstrated by Duan et al (pg 1576, Figure 5).

Oberdorf et al taught that the proteasome comprises chymotrypsin-like, peptidylglutamyl-peptide hydrolyzing or trypsin-like activity, depending upon the β -subunit isoform, that all active proteasome β -subunits participate in substrate degradation, but they do not necessarily contribute equally, and that little is known about the relative contribution of specific β -subunits in the degradation of a particular protein substrate (Abstract; pg 13397, col. 2, ¶1). Oberdorf et al teach the ability to optimize the concentration for each proteasome β -subunit inhibitor (pg 13401, Figure 3; pg 13403, Figure 6), as well as the ability to combine proteasome protease inhibitors to inhibit most, if not all, proteasome activity (pg 13399, Figure 1; pg 13404, Figure 7). Thus, at the time of the invention, those of ordinary skill in the art practiced combining elements [proteasome protease inhibitors] that will perform their expected functions to achieve their expected results when combined for their common known purpose [proteasome protease inhibition].

With respect to the instantly elected embodiments of proteasome protease inhibitors LLnL and doxorubicin, Mikulski disclosed the *in vitro* combinatorial use of doxorubicin and LLnL (col. 3, lines 35-40), thereby demonstrating that LLnL may be used in combination with doxorubicin as part of an agent cocktail.

While the cited prior art does not teach that doxorubicin may be used to enhance rAAV transduction, alone or in combination with LLnL, those of ordinary skill in the art would have a reasonable expectation that such an activity would necessarily flow from doxorubicin's activity in the cell, as evidenced by the proteasome protease inhibitor LLnL demonstrated to enhance rAAV transduction (Duan).

Duan et al do not teach the rAAV express a therapeutic or prophylactic gene product; however, Duan et al teach that AAV vectors are known in the art as a gene therapy vehicle and have been used in strategies conceived for functional correction of the cystic fibrosis transmembrane conductance regulator (CFTR; pg 1573, col. 1, Introduction). Absent evidence to the contrary, nothing non-obvious is seen with substituting the marker gene for a therapeutic or

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prophylactic gene in an AAV vector because the art has long recognized and used AAV vectors for gene therapy.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try combining the proteasome inhibitor LLnL with doxorubicin in a method to enhance rAAV transduction with a reasonable chance of success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this lead to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP §2144.07. In the instant case, an artisan would be motivated to try combining doxorubicin with LLnL in a method to enhance rAAV transduction because both agents are recognized in the art as proteasome protease inhibitors (Duan, Kiyomiya), a person of ordinary skill in the art would have recognized that the results of the combination of proteasome protease inhibitors were predictable (Oberdorf), LLnL and doxorubicin have been combined before in a drug cocktail (Mikulski) and Maitra et al suggest using doxorubicin to increase the expression of CFTR, thereby ameliorating the symptoms of diseased polarized epithelial cells in need of gene therapy via a rAAV encoding a CFTR therapeutic transgene. Thus, the combination of doxorubicin and LLnL would reasonably be expected to cooperate in therapeutic treatment of polarized epithelial cells.

It also would have been obvious to one of ordinary skill in the art to try combining the method of enhancing rAAV transduction as taught by Duan et al in view of Kiyomiya et al and Maitra et al to further comprise contacting the cell with an agent that alters uptake of rAAV at the cell membrane with a reasonable chance of success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this lead to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. Applicant admits that it is likely that EGTA (Duan) altered AAV binding to cell surfaces or internalization (Remarks, pg 22, ¶2), and thus EGTA is the only agent that alters uptake of rAAV at the cell membrane. In the instant case, an artisan would be motivated to try combining

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the method of enhancing rAAV transduction as taught by Duan et al to further comprise contacting the cell with an agent, e.g. EGTA, that alters uptake of rAAV at the cell membrane because Duan et al taught that the combined use of EGTA with LLnL enhanced transduction by at least 10 fold more than either agent alone (pg 1576, Figure 5).

It also would have been obvious to one of ordinary skill in the art to substitute the rAAV vector(s) of Duan et al for the rAAV vectors taught by Englehardt with a reasonable chance of success because at the time of the invention, the art had long-recognized the ability to co-transfect mammalian cells with a mixed rAAV population comprising at least two different rAAV vectors. The simple substitution of one rAAV population for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to use an rAAV population comprising at least two different rAAV vectors because a two-rAAV-vector system based on the prior knowledge in the art regarding the molecular structure of rAAV concatamers may greatly increase the usefulness of rAAV gene therapy vectors for those genes, e.g. CFTR, whose cDNA barely fits into an rAAV vector and whose expression has been hampered by the inefficient promoter activity of the rAAV ITR.

Applicant's invention is predicated on an unexpected result (Remarks, pg 21, ¶2), which typically involves synergism, an unpredictable phenomenon highly dependent upon specific proportions and/or amounts of particular ingredients. Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him/her. The adjustment of particular conventional working conditions (e.g., determining appropriate amounts of such ingredients therein) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (Oberdorf). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant argues that:

a) there is nothing in Kiyomiyo et al related to virus transduction;

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b) there is nothing in Maitra et al related to virus transduction and Maitra et al teach that doxorubicin is “unlikely” to be useful in a clinical setting due to its cumulative systemic toxicity (pg C1037), and thus teach away from the use of doxorubicin *in vivo*;

c) Englehardt is not concerned with administering agents that enhance AAV transduction;

d) there is no combination of the cited documents that discloses or suggests the use of the recited combination of agents to enhance rAAV transduction and, given the disclosure of agents that likely interact with proteosomes in Duan et al. and Kiyomiyo et al;

e) is unexpected that a combination of agents such as those with purportedly the same target would at least additively enhance AAV transduction; and

f) agents that likely interact with proteosomes may be competitors for binding to the proteosome.

Applicant’s argument(s) has been fully considered, but is not persuasive.

With respect to a), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Duan et al teach that cells pretreated with the proteosome protease inhibitors prior to contact with the rAAV results in enhanced transgene expression. Kiyomiyo et al is considered relevant prior art for teaching that doxorubicin is also considered a proteosome protease inhibitor, and thus would likely also enhance rAAV transduction for being another species within the same genus of agents having proteosome protease inhibitor activity.

With respect to b), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Maitra et al is considered relevant prior art for suggesting the use of doxorubicin to enhance CFTR gene expression. As a second matter, Applicant appears to have overlooked that Maitra et al acknowledge that amount of doxorubicin used is approximately 20-fold lower than its LC50, suggesting that one might also be able to achieve these effects *in vivo* at a

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comparably low dose that is well below those used in cancer chemotherapy and that can elicit significant "nontarget" toxicity (pg C1037, col. 1, ¶1), thereby suggesting further optimization of doxorubicin concentration to avoid toxicity yet retain the desired activity. As a third matter, the claims do not recite the amount or frequency of doxorubicin that is to be used *in vivo*, and thus Applicant's argument regarding cumulative toxicity as per the instantly claimed invention is unsubstantiated.

With respect to c), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Englehart is considered relevant prior art as per the structural elements of rAAV vectors, as admitted by Applicant (pg 20, ¶3).

With respect to d), in response to Applicant's argument that the cited documents do not disclose or suggest the use of the recited combination of agents to enhance rAAV transduction, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Applicant is respectfully reminded that the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP §2144.07. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose (as well as to use such a composition for that purpose - i.e., to inhibit proteasome protease activity). The idea for combining them flows logically from their having been used individually in the prior art, and from them being recognized in the prior art as useful

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for the same purpose. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients. *In re Kerkhoven*, 626 F.2d 846, 850, 205 U.S.P.Q. 1069 (CCpA 1980), *In re Sussman*, 1943 C.D. 518; *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423,426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). In the instant case, doxorubicin and LLnL are both art-recognized species of proteasome protease inhibitors (Duan, Kiyomiya), those of ordinary skill in the art had routinely practiced combining different proteasome inhibitors for the same purpose (Oberdorf), and had practiced combining LLnL with doxorubicin to achieve a desired effect (Mikulski). Thus, in light of the knowledge, practice and common sense possessed by the routineer at the time of the invention, the combination of LLnL with doxorubicin would have been obvious.

With respect to e), Arguments of counsel cannot take the place of evidence in the record. See *In re Schulze*, 346 F.2d 500, 602, 145 USPQ 716, 718 (CCPA 1965). Attorney statements regarding unexpected results are not evidence without a supporting declaration.

With respect to f), Arguments of counsel cannot take the place of evidence in the record. See *In re Schulze*, 346 F.2d 500, 602, 145 USPQ 716, 718 (CCPA 1965). Attorney statements regarding a first agent being a potential competitive inhibitor for a second agent is simply without evidentiary support.

8. **Claim 62 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS), Maitra et al (Am. J. Physiol. Cell Physiol. 280:C1031-C1037, 2001; *of record) and Englehardt (U.S. Patent 6,436,392; *of record), as applied to claims 1-2, 4-7, 9-23, 43-44, 46, 48-50, 61 and 63-64 above, and in further view of Voinea et al (J. Cell. Mol. Med. 6(4):465-474, 2002; *of record).

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Determining the scope and contents of the prior art.

Neither Duan et al, Kiyomiya et al, Maitra et al nor Englehardt teach the liposomal formulation of doxorubicin. However, at the time of the invention, Voinea et al taught the use of 'intelligent' liposomes for efficient delivery of drugs, specifically Doxil®, the sterically-stabilized liposomal formulation of doxorubicin (pgs 469-470, joining ¶).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, virology, cellular infection with rAAV, and protocols and reagents useful for the treatment of disease. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute doxorubicin for the liposomal formulation of doxorubicin with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute doxorubicin for the liposomal formulation of doxorubicin because the liposomal formulation provides for decreased toxicity than the naked drug as well as longer circulation times. Furthermore, the artisan may add targeting moieties onto a liposomal formulation so as to further improve the targeting of doxorubicin to the desired cell type.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant does not contest the teachings of Voinea et al as applied to the obviousness of substituting doxorubicin for the liposomal formulation of doxorubicin with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

9. **Claim 24 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS), Maitra et al (Am. J. Physiol. Cell Physiol. 280:C1031-C1037, 2001; *of record) and Englehardt (U.S. Patent 6,436,392; *of record), as applied to claims 1-2,

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4-7, 9-23, 43-44, 46, 48-50 and 61-64 above, and in further view of Hirsch et al (US 2003/0003583; *of record).

Determining the scope and contents of the prior art.

Neither Duan et al nor Englehardt teach the method to comprise the step wherein the cell is contacted with the virus before the cell is contacted with at least one agent. However, at the time of the invention, Hirsch et al disclose a method of infecting mammalian host cells with a rAAV, the method comprising the administration of a proteasome inhibitor, e.g. LLnL (pg 2, [0021]; pg 10, [0117-0128]), wherein the proteasome inhibitors may be administered at any time before, during or after the administration of the virus (pgs 10-11, [0130]).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, virology, cellular infection with rAAV, and protocols and reagents useful for the treatment of disease. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to modify the method of Duan et al to comprise the order of cell contacting steps as taught by Hirsch et al with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements by known methods with no change in their respective functions, and the combination would have yielded predictable results. An artisan would be motivated to contact a cell with a proteasome inhibitor after having contacted the cell with an rAAV virus because it is well within the common sense of the ordinary artisan to

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recognize three delivery combinations—before, during or after—and choosing any one of the three is standard practice when optimizing a method.

Thus, the invention as whole is *prima facie* obvious.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

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